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Non-specific urethritis and the tetracyclines

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Non-specific urethritis (NSU) is treated as an entity, yet it includes cases of urethral inflammation presumed to be related to the presence of probably several specific organisms. The effectiveness of the tetracycline group of antibiotics in comparison with other forms of treatment is not in doubt (Willcox, 1972). In the present study we wish to remark upon the aetiology of NSU and to discover whether tetracycline treatment can assist us in understanding the nature of NSU, and also to comment on the best application of tetracycline therapy.

NSU is generally diagnosed in those cases of urethritis in which the exudate is mainly made up of polymorphonuclear leucocytes and contains no micro-organisms visible in the Gram-stained smear. A proportion of cases contain one or more of a variety of micro-organisms, such as *Chlamydia*, *Mycoplasma*, and bacteria other than gonococci. *Trichomonas vaginalis* and *Candida albicans* may also cause non-gonococcal urethritis. The possible aetiological factors were reviewed by Csonka (1965).

NSU and the main aetiological factors in non-gonococcal urethritis in men

(1) *Allergy*

An allergic urethritis (NSU) may be due to both non-infective and infective factors. Non-infective factors have been suggested in the past as a cause of urethritis. Evidence for the existence of delayed hypersensitivity in patients with NSU was investigated by skin-testing, and the literature reviewed, by Grimble and Csonka (1955). Weston (1965) cited further evidence to support an allergic aetiology of NSU.

The probability that an infective factor might also be involved in an allergic urethritis is supported by the finding of increased serum immunoglobulin levels similar to those occurring in gonorrhoea (Scott and Rasbridge, 1972).

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(2) *Infective agents*

(*a*) *CHLAMYDIA* AGENT

Apart from the occasional recovery of herpes virus, true viruses have not been implicated in NSU although urethritis may sometimes be seen in several virus disorders, such as measles, mumps, and virus hepatitis.

Jones (1972) and Dunlop, Vaughan-Jackson, Darougar, and Jones (1972) have reviewed recent work on the isolation of chlamydial agents. About 45 per cent. of patients with NSU harbour Subgroup A *Chlamydia* (Dunlop and others, 1972). The available methods of isolation, although recently improved, do not, according to Jones (1972), allow us to be certain what proportion of patients with NSU harbour this organism (see also Sompolinsky, Harari, Solomon, Caspi, Krakowski, and Henig, 1973; Wentworth, Bonin, Holmes, Gutman, Wiesner, and Alexander, 1973). Yet the role of this agent, although probably at times a pathogen, is still questionable (Richmond, Hilton, and Clarke, 1972; Hilton, Richmond, Milne, Hindley, and Clarke, 1974; Oriel, Powis, Reeve, Miller, and Nicol, 1974).

It may be that *Chlamydia* agent plays an 'opportunist' role, and acts both as pathogen and as 'potential pathogen' in the genito-urinary tract. Much of this work is relatively new and still continuing. A recent study on the presence of antibodies to *Chlamydia* in patients with urethritis, and in persons without urethritis, does not make the position any clearer (Reeve, Gerloff, Casper, Philip, Oriel, and Powis, 1974).

(*b*) *MYCOPLASMA*

Mycoplasma hominis (and to a much lesser extent *M. fermentans* and *M. salivarius*) and T-strain mycoplasma can be present in those with a healthy genito-urinary epithelium as well as in those in whom the epithelium is inflamed. It would appear from the evidence that the T-strain may be present in over 60 per cent. of cases of urethritis, and *M. hominis* in about 20 per cent. of cases.

The earlier work seemed to implicate mycoplasma as a possible pathogen (Dienes, Ropes, Smith, Madoff, and Bauer, 1948; Morton, Smith and Leberman, 1951; Nicol and Edward, 1953; Berg, Weinberger, and Dienes, 1957; Grimble, 1959, 1968; Klieneberger-Nobel, 1959; Card, 1959). The consensus of opinion was that the organism was a 'potential pathogen'. Further work has both substantiated and failed to verify the earlier results. Those who consider it to be a commensal only include Freundt (1956), Black and Rasmussen (1968), Taylor-Robinson, Addey, Hare, and Dunlop (1969), and Gregory and Cundy (1970).

The role of *Mycoplasma* in genito-urinary disease therefore remains an enigma in its obvious 'opportunism': its presence as a commensal and yet its existence in severe disease states, and also its capacity to stimulate an immune response. The following investigators have provided results that should not be overlooked in this context: Stokes (1955), Jones (1967), Tully and Smith (1968), Sepetjian, Thivolet, Monier, and Salussola (1969), Ford (1969), Mårdh (1970), Mårdh and Weström (1970), Russell and Fallon (1970), Pachas (1970), Shepard (1970), Caspi, Herczeg, Solomon, and Sompolinsky (1971), Hofstetter and Schmiedt (1972), Jansson, Vainio, Lassus, and Tuuri (1972), Hill, Philip, Greaves, and Purcell (1973), McChesney, Zedd, King, Russell, and Hendley (1973), McCormack, Braun, Lee, Klein, and Kass (1973), Kundsin, Parreno, and Kirsch (1973), Boe, Diderichsen, and Matre (1973), Sompolinsky and others (1973), Wentworth and others (1973). In severe disease and in septicaemic conditions, Solomon, Caspi, Bukovsky, and Sompolinsky (1973) isolated *M. hominis* more commonly than T-strain. The relation of *M. hominis* to reproductive failure (Kundsin and Driscoll, 1970) and to respiratory tract infection (Mufson, 1970), and the recent evidence for T-strain colonization of sperm (Gnarpe and Friberg, 1972, 1973) are also pertinent.

(*c*) BACTERIAL CAUSES

There is no firm evidence for the involvement of specific bacteria in NSU, nor in fact for mildly pathogenic and commensal bacteria. The bacterial causes of NSU were reviewed by Harkness (1950). Furness and Csonka (1966) isolated *Corynebacteria*, and Kozub, Bucolo, Sami, Chatman, and Pribor (1968) reported the presence of a non-motile Gram-negative rod (*Mimea polymorpha, var.* oxidans) in the urethral discharge of patients with urethritis. Inability to grow certain bacteria of low-grade pathogenicity, and the failure to investigate L-forms, may be due to unsuitable culture media. *Corynebacteria* and *Haemophilus* have received only slight attention (Lee and Schmale, 1973; Carney, 1973; Furness, Kamat, Kaminski, and Seebode, 1971, 1973).

(*d*) *TRICHOMONAS VAGINALIS*

This causes infection in the lower genital tracts of both men and women, and the infection is sexually transmitted. Often *T. vaginalis* is found in the absence of any clinical symptoms. The morphology of this organism has been studied by Feinberg (1954).

The incidence of *T. vaginalis* in males with urethritis has been studied by a number of workers (Feo, Varano, and Fetter, 1956: Symposium on Trichomonal Infestations, 1957; Lanceley, 1953, 1958; Burgess, 1959; Rosedale, 1959; Sylvestre, Belanger, and Gallai, 1960; Willcox and Rosedale, 1962, Wisdom and Dunlop, 1965). From these studies it is apparent that the incidence of trichomonal urethritis in the male is variable. The consensus of opinion in the United Kingdom is that its incidence in men with non-gonococcal urethritis is approximately 10 to 15 per cent. The apparent incidence in the male rises with the care and length of time that is given to its isolation. In one clinic (personal communication from Dr. M. A. E. Symonds), the incidence of *Trichomonas* in abacterial urethritis is 15 per cent. and the organism is isolated in over half of the male consorts of women with trichomoniasis.

(*e*) GENITAL CANDIDOSIS

This has been investigated by Winner and Hurley (1964) and reviewed by Rohatiner (1966). Rohatiner found that, in male consorts of women with candidosis, 7 per cent. of the men had urethritis containing yeasts, and over 54 per cent. had NSU. The cause of this high incidence was discussed. *Candida* cystitis has been discussed by Zinke, Furlow, and Farrow (1973). The significance of circulating antibody has more recently been investigated by Stanley, Hurley, and Carroll (1973) and Dolan and Stried (1973).

(3) *Non-specific factors*

Whatever these non-specific factors are, whether traumatic, irritant, or partly arising from "excessive use", it is apparent from clinical experience, and from the facts of this study, that a proportion of cases of NSU arise when there is no ascertainable abnormality (other than the anterior urethritis) in either the man or the woman. This can be seen from the results of a particular group in this study (see Table III and Discussion). Siboulet (1960) considered that half of his cases required psychotherapy, and that physical causes were not solely responsible.

Tetracycline in the treatment of NSU

The tetracyclines are a group of wide-spectrum antibiotics having differing diffusion and excretion rates within the group. The common ones in use at present are: oxytetracycline hydrochloride, a triple tetracycline compound (tetracycline-chlortetracycline-demethylchlortetracycline 1:1:0·6), and tetracycline hydrochloride. It is well to recall here that,

although these antibiotics are relatively free from side-effects, there can be undesirable reactions (see Martindale, 1972).

The usefulness of the tetracyclines in the treatment of NSU strongly suggests that an infective factor is operating in a significant proportion of cases. That the tetracyclines are the most useful antibiotic therapy also points to their having some antimicrobic property in superior measure to other antibiotics and to the sulphonamides. This property would appear to lie mainly in their ability to act more completely on *sub*bacterial forms. The antibacterial spectra of tetracycline, ampicillin, and sulphonamide, for example, are not widely different, yet the clinical effects of these drugs in the treatment of NSU are very different.

The chemotherapy of chlamydial infections was reviewed by Jawetz (1969), who found that the results revealed a wide range of susceptibility of different clinical isolates: to quote, 'most observations indicate that tetracyclines suppress chlamydial growth but fail to eliminate the agent from an infected host'. Tetracycline is the most useful antibiotic in the treatment of trachoma; yet the optimal dosage for the treatment of clinical chlamydial infection is uncertain. It has been suggested from experimental studies in ocular chlamydial infection, that the action of tetracycline may partly operate by diminishing 'secondary infection' and thus by affecting the ability of *Chlamydia* to thrive (Jawetz, Hanna, Dawson, Wood, and Briones, 1967; Dawson, Hanna, and Jawetz, 1967).

Material and criteria for the trials

The diagnosis of NSU was made in the usual way by the appearance of abacterial pus in a Gram-stained smear. Yeasts were excluded, as was *Trichomonas vaginalis*, in a wet preparation. Only those cases with a first-glass urinary haze, or solid aggregates or profusion of flakes indicating a fresh urethral infection were included in the trials. Patients with long urinary threads were excluded, since this sign can indicate a complicating inflammatory condition of the ducts and glands. One hundred patients were included in each category in each scheme of treatment. The patients were seen after 1 week and 2 weeks, and if possible at 2-week intervals subsequently. A satisfactory response was established by the absence of discharge and a completely clear urine in both glasses when the urine had been held for more than one hour (usually 2 to 3 hours). Any flakes, or light mucus, in the urine were accounted a sign of failure to respond.

The present investigation consisted of four trials in succession:

(1) Oxytetracycline, 0·25 g. four times a day for 4 days and for 10 days to alternate patients:

(2) A triple tetracycline compound,* 0·3 g. twice daily for 4 days and for 10 days to alternate cases.

(3) The third trial was planned using triple tetracycline and a placebo. 0·6 g. triple tetracycline was given twice daily for 7 days, when in the second trial it was apparent that 10-day courses were marginally more successful than 4-day courses. The placebo was made up to resemble triple tetracycline by the manufacturers, and was given to alternate cases (2 tabs twice daily for 7 days).

(4) Tetracyline 0·25 g. four times a day and 0·5 g. four times a day for 7 days, was given to alternate patients.†

Since NSU is often a relatively mild disorder, it was considered that the use of tetracycline for 3 weeks in every case might not be appropriate. We therefore did not use a prolonged course of treatment in many cases. However, we were able to analyse the results of such a 21-day course used routinely by a colleague; Dr. Fluker kindly allowed one of us (who had worked in his department) to examine the results at the West London Hospital and contrast them with our own. The use of the drug for 3 weeks by us in a few cases did not result in an increased success (see Table I, footnote).

*'Deteclo', manufactured by Lederle Laboratories. Each film-coated tablet is stated to contain chlortetracycline HCl 115·4 mg., tetracycline HCl 115·4 mg., and demethylchlortetracycline 69·2 mg.
†Several patients in this last trial complained of alimentary side-effects with the larger dose of drug.

TABLE I *NSU trial: results of four successive comparisons using different courses of treatment 100 patients were treated by each treatment schedule*

Treatment			*Result*		
Schedule	*Drug*	*Dosage*	*Responded within 2 weeks*	*Unresponsive*	*Defaulted*
1	Oxytetracycline	250 mg. four times daily for 4 days	68	—	32
		250 mg. four times daily for 10 days	73	—	27
2	Triple tetracycline	1 tab. (300 mg.) twice daily for 4 days	52	12	36
		1 tab. twice daily for 10 days	66	4	30
3	Triple tetracycline	2 tabs twice daily for 7 days	72	13	15
	Placebo	2 tabs twice daily for 7 days	20	73	7
4	Tetracycline	250 mg. four times daily for 7 days	58	20	22
		500 mg. four times daily for 7 days	61	22	17
West London Hospital*	Oxytetracycline	250 mg. four times daily for 21 days	68 (within 3 weeks)	4	28

*Of eight cases of NSU treated in the Guy's clinic with triple tetracycline, 1 tab. twice daily for 21 days, four were clear at the end of this period and four had not responded.

Results

The results of the trials are shown in Table I. The response to the tetracyclines, when strict criteria of cure are applied 2 weeks from the start of treatment, is less good on the whole than some reports lead one to suppose (Willcox, 1972; Bhattacharyya and Morton, 1973). It is common experience, however, to find that a proportion of cases spontaneously recover over a period of several weeks. Thus a better response to treatment will naturally appear to have taken place the longer the follow-up (see Fowler, 1970; and Discussion below).

The results with tetracycline were not quite as satisfactory, in this study, as those with triple tetracycline and the 4- or 10-day course of oxytetracycline (Table I).

The cases receiving the placebo showed a 20 per cent. recovery rate. The recovery was usually noted within a short period after the start of treatment. A very few cases on the placebo therapy became markedly worse towards the end of their week's course. The fact of differing types of response such as these seemed well enough defined to suggest in itself the existence of clinically distinct entities within the group labelled 'NSU'.

It was also noteworthy that there were fewer defaulting cases in the placebo-treated group. This suggests that many of the cases defaulting after treatment with the tetracyclines may well have done so for reasons of satisfactory recovery.

Prolonged therapy: 21-day treatment

The 21-day course did not show superior results to treatment with shorter courses of the tetracyclines (see Table I), in contrast to the findings reported by John (1971) and Bhattacharyya and Morton (1973). A small series of patients were treated by us with a 3-weeks course of triple tetracycline to see how this compared with the West London results. The results (shown in the footnote to Table I) did not indicate that the 21-day course would be superior in our hands to the other courses used in the trials.

Amongst the female consorts examined, just less than two-thirds had non-specific vaginitis; *Trichomonas* was isolated in 12 per cent. and *Candida* more frequently. Significantly, all the consorts of men who responded to the placebo were healthy, both clinically and bacteriologically.

In an attempt to throw some light on the question of the infective *versus* non-infective factor in the aetiology, a selected group of women consorts of a special category of men with NSU was also examined. The women were the ONLY consorts of this group of men, men who had NOT had a previous attack of NSU or any other genito-urinary disorder (see Table II). Of the 110 women thus examined, 11 per cent. had a trichomonal infection, in 29 per cent. *Candida* was present, and in 45 per cent. there was a vaginitis; 33·5 per cent., however, were entirely normal with regard to the appearance of the vaginal epithelium and cervix, and the bacterial flora (Table II). It is our experience that the vaginal bacterial flora changes rapidly when infection with *Mycoplasma*, *Candida*, or *Trichomonas* occurs.

Discussion

The results of these trials were not unexpected, and it would be well to discuss four aspects in particular:

(1) The way in which the tetracyclines are used in NSU;

(2) The light that is shed on the possible aetiological factors;

(3) The meaningfulness of the term 'non-specific urethritis', and the natural history of this disorder;

(4) The female consorts of men with first attacks of NSU.

(1) Although tetracycline itself is said to be therapeutically more effective than 'oxy'- and 'chlortetracycline', the latter are usually prescribed. From the evidence of this trial, the most effective drug at present in common use in NSU seems to be either triple tetracycline (Deteclo) or oxytetracycline. The effectiveness of the tetracyclines in this study lies

TABLE II *Results of examination of female consorts of selected men with NSU, who had no previous urethritis or other genito-urinary disorder, and only one consort*

Grossly abnormal bacterial flora (A)	*Intermediate (B)*	*Normal lactobacilli (C)*	Trichomonas vaginalis	Candida	*Total number of patients*
31	7	37	12	32 { 16 (A) flora; 13 (B) flora; 3 (C) flora }	110

i.e. 31 (28 per cent.) had non-specific vaginitis
12 (11 per cent.) had trichomonal infection with or without *Candida*
16 (14·5 per cent.) had vaginitis plus *Candida*
32 (29 per cent.) had *Candida* present with or without vaginitis
37 (33·5 per cent.) were healthy.

in their ability to produce cure in about ⅔ or more of those followed-up for 2 weeks (Table I). The rate of response of NSU to treatment with the tetracyclines did not vary startlingly whichever type of drug or schedule of treatment was used.

As already mentioned, NSU is sometimes so mild a condition that a prolonged course of a tetracycline would seem to be disproportionate to the severity of much of the urethritis being treated. It seems to us that, on the evidence, shorter courses or repeated courses are preferable. In our series the results with shorter courses were not dissimilar to the results of the long course of 21 days which we analysed, and our use of a 21-day course at Guy's gave poorer results. From the results of using a placebo it can be stated that at least 20 per cent. of cases of NSU in this trial recovered spontaneously within two weeks (a smaller figure than Fowler obtained—see Discussion 3).

What is clear from these figures (as well as those of Fowler (1970)) is that of those who apparently responded to a tetracycline, at least 20 per cent. (see below) had cleared up spontaneously. It would seem, therefore, that we are left with approximately 50 per cent. of all cases of NSU as capable of benefiting directly from tetracycline within 14 days of starting therapy.* Fowler (1970) puts the figure of those so benefiting at 35 per cent. (see Discussion 3).

Those cases which do not respond to treatment with a tetracycline may consist of infection with insensitive organisms, such as the *Trichomonas*, or of non-infective inflammation. Although trichomoniasis was excluded (so far as possible) before treatment, some of the consorts were found to harbour *T. vaginalis*. The sample examined by us was small; but *T. vaginalis* was isolated in 12 per cent. of consorts of tetracycline-treated cases of NSU. Approximately the same incidence occurred in the consorts of the placebo-treated cases of NSU. It is well known that, when a case of proved trichomoniasis in the male is treated with metronidazole, tetracycline is sometimes required before the inflammation clears up satisfactorily. There would therefore appear to be another factor as well as the presence of *T. vaginalis* in such cases.

(2) What is being treated? Tetracycline is likely to be fully effective in average doses against mycoplasmal or secondary bacterial infection in non-gonococcal cases. These organisms usually respond, if at all, to comparatively short courses of treatment. Although *Mycoplasma* organisms,‡ especially the T-strain, are present in urethritis, their role as pathogen is uncertain. Commensal and other bacteria play an even more uncertain role. Whether the effect of tetracycline on *Chlamydia*‡ in the genito-urinary tract is rapidly curative or not, in the dosages given here, is also uncertain.

There also remains doubt concerning the role of *Chlamydia* in urethritis, and its sensitivity to tetracyclines. But it is in this group of cases that increased amounts of treatment might be expected to lead to improved results. As already mentioned, however, the effectiveness of a 21-day course of treatment in our cases does not reveal the superiority over short courses that would be expected were such an infecting agent the major cause of the disease (Table I) (that is, unless this particular agent were fully sensitive to moderate amounts of tetracycline). Such behaviour makes the exact relationship of the *Chlamydia* to the urethritis a difficult matter to unravel.

Evidence for a multiple infective, non-specific, or non-infective causation of the inflammation in a significant proportion of these cases arises from several sources. First, there are the results of several workers (Tables IIIA and IIIB) demonstrating multiple isolations. Wentworth, Bonin,

TABLE IIIA *Isolations from urethritis in men* (115 *cases*) (*Somplinsky and others*, 1973)

Diagnosis	*Per cent.*
Chlamydia	52
Mycoplasma T-strain *M. hominis*	63 16
Cytopathogenic viruses (67 cases tested)	0
Non-gonococcal urethritis (78 cases tested)	63 *Chlamydia* 65 *Mycoplasma*
Gonorrhoea	32 (*Chlamydia* 30, *Mycoplasma* 65)
Negative for all above organisms	9
Controls (28 cases)	T-strains from two cases, with *M. hominis* also in one. *Chlamydia* + polymorphs in one case

TABLE IIIB *Percentage isolations of different organisms from cervix*

Organism	*Simultaneous isolations of several different organisms from the cervix* (*Wentworth and others*, 1973)	*Isolations from the cervix of teenage girls in a venereal disease clinic* (61 *cases*) (*Sompolinsky and others* (1973)
Chlamydia	21·5	34·0
Mycoplasma, T-strain *M. hominis*	84·7 45·9	75·0 (25% in throat)
Trichomonas vaginalis	17·0	23·0
Cytomegalovirus	23·4	—
N. gonorrhoeae	16·7 (*Chlamydia* 7%)	11·0

*Roughly 30 per cent. will not do so and 20 per cent. clear up spontaneously.

‡*M. hominis* 20%, T-strain 60–70%; *Chlamydia* 40%

Holmes, Gutman, Wiesner, and Alexander (1973) state from their experience with isolations in women: 'The data show that none of these agents tended to occur alone and all were found more frequently in the presence of other agents than as single isolates'. This suggests a multiple infective aetiology in many instances, and such may also be the case in men. Secondly, the results of the placebo trial (see below (3) and Table I) and the results of examining the consorts when a proportion of the women, who were the sole consorts of the men, were clinically healthy and had a normal bacterial flora (Table II), suggest a non-specific or even a non-infective aetiology in a proportion of cases.

(3) The knowledge that between 20 and 34 per cent. of cases of NSU clear up spontaneously in approximately 2 weeks, brings us to another question: Is it always necessary to treat all cases of NSU energetically? Fowler (1958, 1970, and personal communication of current work) discussed this matter and investigated the natural history of the disease. There was no evidence of urethritis 14 days after starting a 4-day course of tetracycline in 72 per cent. of Fowler's cases (a figure very similar to the results in this present trial). His spontaneous cure rate, however, using lactose as placebo, was 34 per cent. at 2 weeks. He found that recurrence of the urethritis after 2 weeks was commoner in the tetracycline-treated group than in the group treated with the placebo lactose. But recurrences, he noted, were less frequent in the tetracycline-treated group when higher dosage was used. Table IV, which also includes his unpublished observations, is worth studying in the light of the present discussion.

TABLE IV *Spontaneous cure*

Recovery rate in NSU using Placebo treatment :
Fowler (1970)—34 per cent.
Present study —20 per cent.

Observations on the course of untreated NSU (after Fowler, 1970 and personal communication)

(1) Over nine out of ten cases asymptomatic within 1 week,
(2) 20 per cent. of all cases recover spontaneously within 1 week,
(3) 34 per cent. of all cases recover spontaneously within 2 weeks ;
(4) 25 per cent. present no further discharge after 2 weeks but urinary signs persist ;
(5) 24 per cent. have a persistent discharge exceeding 3 weeks ;
(6) 6 per cent. have a persistent discharge exceeding 3 months.

In 50 per cent. of those cases with persistent discharge ((5) and (6)) the condition is unaffected by tetracycline

Perhaps a minimal incidence of one type of NSU (*i.e.* 20 per cent.) is to be found in the cases who were treated with the placebo in the present trial and recovered rapidly. As stated above, the consorts of this type of case when examined were normal.

Those cases of NSU which failed to respond to the initial treatment usually but not invariably fared well on further therapy with the same drug for a limited period of 5 to 7 days. A small number responded to metronidazole.

'Non-specific urethritis' as a term may imply several things. First it can mean that the condition occurs without a background of any specific micro-organism. Secondly, it could cover those cases in which mixed factors, or a mixed flora of infecting micro-organisms rather than one, predominated in the aetiology. Research has failed to demonstrate conclusively that any one organism is capable of causing this type of urethritis.

We are therefore left with the impression that mixed factors and a mixed flora, mainly sub-bacterial, exist in the background of many cases of this 'non-specific' urethritis, and that the tetracyclines will help about 50 per cent. of them (or 35 per cent. according to Fowler (1970)) towards recovery. Among these will be the cases from which *Chlamydia*. secondary bacteria or L-forms, and *Mycoplasma* (T-strain principally but perhaps also *M. hominis*) can be isolated.

Those not directly affected by therapy may be cases of *Chlamydia* urethritis, non-specific non-infective urethritis, *Trichomonas* or *Candida* urethritis, and so forth.

Non-infective cases, as already stated, almost certainly exist, as suggested by the rate of spontaneous recovery and the figure for the incidence of urethritis when the consort is healthy (33 per cent.). Trauma or 'physiological excess' is not so unlikely a factor.

(4) Women who were the ONLY consorts of men who had had NO previous attack of NSU or other genito-urinary disorder were selected for a special investigation. The clinical condition of this group of women was considered more likely to throw light on the related NSU in the men and on the aetiological factors involved.

It was noticeable that the majority of these women had an inflammatory condition, or abnormality, albeit mild in many cases. Yet it is important to note, in reverse, that women would come to the clinic for investigation of symptoms, or with some anxiety, and also present with similar inflammatory or abnormal genital conditions yet state that their male consorts were healthy.

The consorts of the cases of NSU which responded to the placebo were normal.

Over half the women in the group of 110 consorts had signs of an unhealthy condition in the vagina and/or cervix (including those harbouring the *Trichomonas*) (see Table II). Cervicitis occurred with or without vaginitis. Non-specific vaginitis was diagnosed when there was a grossly abnormal bacterial flora, whether or not *T. vaginalis* or *C. albicans* was also present. 53·5 per cent. had

vaginitis; 11 per cent. together with the *Trichomonas* and 14·5 per cent. with *Candida*. Cervicitis of some degree was present in most women who had vaginitis and in the 20 per cent. of those who were in the 'intermediate' category (see Table II). Beside these data should be set those (see Table IIIB) of Sompolinsky, Harari, Solomon, Caspi, Krakowski, and Henig (1973), Wentworth and others (1973) and Solomon, Caspi, Bukovsky, and Sompolinsky (1973) depicting the frequency of *Chlamydia* and *Mycoplasma* in this type of case and the presence of 'multiplicity' of organisms. 33·5 per cent. of the present group were healthy.

Very little work has been undertaken on the role of non-specific vaginitis with an abnormal flora (or even the normal for that matter), or that of cervicitis (other than gonococcal and chlamydial cervicitis) in relation to genito-urinary infection in men. There would appear to be room for further studies.

Summary

The possible aetiological factors in non-gonococcal and non-specific urethritis are reviewed. The response of NSU to various courses of different tetracycline drugs is assessed. Prolonged courses of treatment did not give better results than shorter courses. When reviewing the infective aetiology of non-gonococcal urethritis, it was noted that more than one organism (or potential pathogen) would be present in many cases. It is therefore surmised that there may be at times a mixed aetiology and at other times a truly non-specific aetiology. Isolations by different workers have indicated that the following organisms might be expected: *Chlamydia* 40 per cent.; *Mycoplasma–M. hominis* 20 per cent., T-strain over 60 per cent.; *Trichomonas* 15 per cent.; *Candida* possibly over 5 per cent. Truly non-specific urethritis may account for 25 to 30 per cent. of cases.

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